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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,874	11/03/2003	Arthur Kunz	AM100788 P1	4900

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/699,874	**Applicant(s)** KUNZ ET AL.	
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 December 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): see attached.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *145-149*.
   Claim(s) rejected: *113-116,118-121,124-127,130,131,133-135,142 and 143*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: see attached.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 12/21/2007 in response to the previous Non-Final Office Action (7/25/2007) is acknowledged and has been entered.

Claims 113-116, 118-121, 124-127, 130-131, 133-135, 142-143 and 145-149 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of claim 144 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of Applicants amendments to the claims.

The rejection of Claims 113-116 and 122-123 under 35 U.S.C. 112, first paragraph, Enablement, is withdrawn in view of Applicants amendments which recite that the proliferative disorder is a B-cell malignancy.

Rejections Maintained:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 113 remains rejected under 35 U.S.C. 102(b) as being anticipated by Ghetie et al. (Blood 1992; 80: 2315-2320, of record) as evidenced by Newton et al. (Blood 2001; 97: page 528-535, of record).

Ghetie et al. teach a method of treating a lymphoma, comprising administering a therapeutically effective amount of a cytotoxic drug/carrier conjugate referred to as RFB4-

dgA, wherein the cytotoxic drug is deglycosylated ricin A chain and the carrier is an antibody directed against the CD22 antigen (page 2317, , 1st column, 2nd to last sentence bridging 2nd column and Table 3). Moreover, the reference teaches a method of treating disseminated Daudi lymphoma comprising administering a therapeutically effective amount of the immunologic conjugate RFB4-dgA with an antibody directed against the CD19 antigen, wherein the combination of the anti-CD19 antibody and immunologic conjugate had significant antitumor activity (abstract and page 2318, Table 6). With regards to the administration, Ghetie et al. teach that the immunologic conjugate was administered retroorbitally (page 2316, 1st column, *IT therapy*). Thus, while Ghetie et al. do not explicitly teach that Daudi lymphoma is a B cell malignancy, the claimed limitation does not appear to result in a manipulative difference in the prior arts method because as evidenced by Newton et al. Daudi lymphoma are human B-cell tumors (page 531, 1st column, 2nd full paragraph). See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

In response to this rejection, Applicants contend that since Ghetie et al. does not teach a cytotoxic drug/carrier conjugate having a low conjugated fraction below 10 percent, Ghetie does not teach the claimed invention. In particular, Applicants assert that the composition used in the claimed methods with its reduced low conjugated fraction below ten percent has a different physical characteristics that is not described in Ghetie et al. nor is it inherent from Ghetie's teachings.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions that Ghetie et al. does not teach all of the claimed limitations, the Examiner acknowledges and does not dispute Applicants assertions that Ghetie et al. does not explicitly teach that the prior art's cytotoxic drug/carrier conjugate has a low conjugated fraction below 10 percent. However, the Examiner recognizes that Applicants have not provided a patentable difference between the prior arts conjugate and the conjugate since it appears that low conjugated fraction below 10 percent is a property of the method of producing the cytotoxic conjugate and not the physical property or chemical properties as asserted by Applicants. For example, the specification teaches that the present inventions discloses an improved conjugation process for the production of the conjugates that resulted in significantly lower levels of the LCF (below 10 percent) without any

significant alteration of the physical or chemical properties (page 4, lines 21-24). In view of this, Applicants assertions that the claimed composition has different physical characteristics that is not described in Ghetie et al. appears to contradict the teachings of the specification of a cytotoxic conjugate without any significant alteration of the physical or chemical properties.

Claims 113-116 and 118-121 remain rejected under 35 U.S.C. 102(b) as being anticipated by Uhr et al. (US 5,686,072, 1997, of record).

Uhr et al. teach a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of a combination of an anti-CD19 antibody and anti-CD22 immunotoxin, wherein the B cell malignancy includes, but is not limited to, leukemia and non-Hodgkin's lymphoma (column 2, lines 48-54 and column 6, lines 16-21). With regards to the patient, the patent teaches that the patients include, but are not limited to, humans (column 6, lines 56-57). With regards to the administration, the patent teaches that the combination can be administered intravenously (column 12, lines 1-2).

In response to this rejection, Applicants contend that since Uhr et al. does not teach a cytotoxic drug/carrier conjugate having a low conjugated fraction below 10 percent, Uhr et al does not teach the claimed invention. In particular, Applicants assert that the composition used in the claimed methods with its reduced low conjugated fraction below ten percent has a different physical characteristics that is not described in Uhr et al. nor is it inherent from Uhr et al's teachings.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions that Uhr et al. does not teach all of the claimed limitations, the Examiner acknowledges and does not dispute Applicants assertions that Uhr et al. does not explicitly teach that the prior art's cytotoxic drug/carrier conjugate has a low conjugated fraction below 10 percent. However, the Examiner recognizes that Applicants have not provided a patentable difference between the prior arts conjugate and the conjugate since it appears that low conjugated fraction below 10 percent is a property of the method of producing the cytotoxic conjugate and not the physical property or chemical properties as asserted by Applicants. For example, the specification teaches that the present inventions discloses an improved conjugation process for the production of the conjugates that resulted

in significantly lower levels of the LCF (below 10 percent) without any significant alteration of the physical or chemical properties (page 4, lines 21-24). In view of this, Applicants assertions that the claimed composition has different physical characteristics that is not described in Uhr et al. appears to contradict the teachings of the specification of a cytotoxic conjugate without any significant alteration of the physical or chemical properties.

Claims 113-116 and 118-121 remain rejected under 35 U.S.C. 102(b) as being anticipated by Goldenberg (US 6,183,744, 2001).

Goldenberg teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). For example, the patent teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, the patent teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias, and acute lymphatic leukemias (column 11, lines 8-11). Regarding the therapeutic agent of the immunoconjugate, the patent teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs (column 12, lines 61+). With regards to the administration, the patent teaches that the immunoconjugates can be administered intravenously (column 14, lines 8-15).

In response to this rejection, Applicants contend that since Goldenberg does not teach a cytotoxic drug/carrier conjugate having a low conjugated fraction below 10 percent, Goldenberg does not teach the claimed invention. In particular, Applicants assert that the composition used in the claimed methods with its reduced low conjugated fraction below ten percent has a different physical characteristics that is not described in Goldenberg nor is it inherent from Goldenberg's teachings.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions that Goldenberg does not teach all of the claimed limitations, the Examiner acknowledges and does not dispute Applicants assertions that

Goldenberg does not explicitly teach that the prior art's cytotoxic drug/carrier conjugate has a low conjugated fraction below 10 percent. However, the Examiner recognizes that Applicants have not provided a patentable difference between the prior arts conjugate and the conjugate since it appears that low conjugated fraction below 10 percent is a property of the method of producing the cytotoxic conjugate and not the physical property or chemical properties as asserted by Applicants. For example, the specification teaches that the present inventions discloses an improved conjugation process for the production of the conjugates that resulted in significantly lower levels of the LCF (below 10 percent) without any significant alteration of the physical or chemical properties (page 4, lines 21-24). In view of this, Applicants assertions that the claimed composition has different physical characteristics that is not described in Goldenberg appears to contradict the teachings of the specification of a cytotoxic conjugate without any significant alteration of the physical or chemical properties.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 124-127, 130-131, 133 and 142-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (US 6,183,744, 2001), as applied to claims 113-116 and 118-121 above, in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588, of record).

Goldenberg teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent (column 4, lines 25-26 and column 11, lines 5-8). For example, the patent teaches that anti-CD22 antibody immunoconjugates can be used to treat both

indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14). In addition to Non-Hodgkin's lymphoma, the patent teaches that the immunoconjugates are useful for the treatment of chronic lymphatic leukemia's, and acute lymphatic leukemia's (column 11, lines 8-11). Regarding the therapeutic agent of the immunoconjugate, the patent teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs pyrimidine analogs, purine analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes and hormones (column 12, lines 61+). With regards to the administration, the patent teaches that the immunoconjugates can be administered intravenously (column 14, lines 8-15).

Goldenberg does not explicitly teach that the therapeutic agent portion of the conjugate is the antibiotic, calicheamicin.

Trail et al. teach monoclonal antibody drug conjugates in the treatment of cancer. Specifically, the reference teaches that members of the enediyne family of antibiotics such as calicheamicin are among the most toxic antitumor compounds described to date, but there utility as antitumor dugs has-for the most part-been limited by their low therapeutic index (page 584, 2nd column, last sentence to page 585, 1st column). Trail et al. further teach that anti-body directed delivery provides a potential means to exploit the impressive potency of these compounds while minimizing their systemic toxicity (page 585, 1st column, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use calicheamicin, a species of antibiotics, in the method taught by Goldenberg in view of Trail et al. teachings that calicheamicin are among the most toxic antitumor antibiotics described to date. One would have been motivated to do so because Trail et al. teaches that antibody-directed delivery of calicheamicin provides a potential means to exploit this impressive potency while minimizing their systemic toxicity. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody, one would achieve an effective method of treating a B-cell malignancy.

In response to this rejection, Applicants assert that it is not routine practice to treat a subject with a B-cell malignancy by administering a composition comprising a cytotoxic

drug-antibody conjugate, including a calicheamicin-anti-Cd22 antibody conjugate, alone or with one or more cytotoxic or bioactive agents. For example, Applicants submit that Trail et al., cited by the Examiner, states on page 586:

> "Although immunoconjugates are not currently established chemotherapeutic agents, several of them have demonstrated evidence of biologic activity in patients with advanced disease. The current objectives are aimed at improving the efficacy and therapeutic index of immunoconjugates by optimizing selectivity and potency ..... The calicheamicin conjugate CMA-676 [5oe] has shown encouraging data in a Phase I trial of patients with refractory AML. Although immunoconjugates may be active as single agents, it is likely that their major role - especially in treatment of solid tumors - will be in combination-chemotherapy regimens or minimal-disease settings. In addition to research efforts directed at improving immunoconjugate constructs, clinical studies to define optimal therapeutic strategies are underway and will further clarify the role of immunoconjugates as anticancer agents." [emphasis added]

In particular, Applicants submit that the calicheamicin conjugate CMA-676 is also referred to as MYLOTARG and was approved by the FDA on May 17, 2000 for the treatment of CD33 positive acute myeloid leukemia and continues to be the only approved antibody-targeted chemotherapeutic agent. In addition, Applicants submit that there have been a variety of calicheamicin conjugates produced, but only limited evidence of activity in clinical trials exists, see for example CMB-401, an anti-MUC1 calicheamicin conjugate discussed in Hinman et al. Cancer Res., 1993, 53, 3336-3342. Similarly, Applicants contend that a paper authored by Hamann et al. (Bioconjugate Chem., 2002, 13, 40-46) provides additional evidence that it is incorrect to assume that one of ordinary skill in the art would have a reasonable expectation of success of achieving an effective method of treatment in a subject with a B-cell malignancy by administering a conjugate comprising calicheamicin and an anti-CD22 antibody. For example, Applicants assert that the in Hamann et al., the authors discuss a comparison of two classes of calicheamicin conjugates made with an anti-CD33 antibody and a MUC1 antibody. In particular, Applicants assert that the authors concluded that:

> "The combined results for these two antibodies indicate that one optimal design of conjugate does not exist for all antibodies. Each antibody must be examined separately, and a variety of different types of conjugates must be tried in order to individually optimize a specific delivery system. The contrasting results obtained with the anti-P67.6 and anti-MUC-1 antibody conjugates probably depend more on the physiology of the

> target cells and the antigen that is targeted than on any specific properties of the antibodies or cytotoxic agent."

Applicants further assert that the review article by Saijo in Cancer Science, 2004, 95, 772-776, cited by the Examiner in the prior Office Action dated August 17, 2006, further undermines the Examiner's assertion that one of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success that a subject with a B-cell malignancy could be effectively treated with a composition comprising calicheamicin-anti-CD22 antibody conjugate alone or in combination with one or more cytotoxic or bioactive agents. In particular, Applicants submit that Saijo's review highlights the high failure rate of molecular target based cancer drugs in phase III human clinical trials, even though preclinical results for these potential cancer drugs were positive. As such, Applicants assert that neither Goldenberg nor Trail et al. teach or describe a method as claimed, but, at best provide a motivation to try to develop a method to treat subjects with a B-cell malignancy by administering a composition a calicheamicin –anti-CD22 antibody conjugate alone or in combination with one or more cytotoxic or bioactive agents.

These arguments have been carefully considered, but are not found persuasive.

First, it is noted that Applicants have extensively argued that it is not routine practice to treat a subject with a B-cell malignancy by administering a composition comprising a cytotoxic drug-antibody conjugate, including a calicheamicin-anti-CD22 antibody conjugate, alone or with one or more cytotoxic or bioactive agents; and therefore, no reasonable expectation of success, without specifically commenting on the teachings of cited combination. However, the Examiner recognizes that it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, Goldenberg teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective

amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent and includes but is not limited to cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs pyrimidine analogs, purine analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes and hormones, but does not explicitly teach that the therapeutic agent portion of the conjugate is the antibiotic, calicheamicin. However, Trail et al. provides the motivation to modify the antibody-conjugate as taught by Goldenberg with calicheamicin because antibody-directed delivery of calicheamicin provides a potential means to exploit its impressive potency while minimizing their systemic toxicity. Thus, in view of the combination of the cited references, one of skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody, one would achieve an effective method of treating a B-cell malignancy. Applicants are reminded that obviousness does not require absolute predictability, see MPEP 2143.02. Secondly, it is noted that Applicants assertions appear to be based on the fact that the FDA has only approved one antibody-targeted chemotherapeutic agent and that only limited evidence of activity for calicheamicin-antibody conjugates exist in clinical trials. While the Examiner does not dispute these arguments, the Examiner recognizes that the Patent Office is not the FDA and does not follow the same criteria that the FDA uses in order to approve a drug for treatment of a particular disease. In the instant case, those of skill in the art recognize, in view of the teachings of Goldenberg, that cytotoxic agent-anti-CD22 antibody conjugates are used for the treatment of B-cell malignancies, wherein therapeutic agents such as chemotherapeutic agents can be linked to the anti-CD22 antibody for site specific delivery of the chemotherapeutic agent to B-cell malignancies, and further, in view of the teachings of Trail et al., that the enediyne family of antibiotics such as calicheamicin are among the most toxic antitumor compounds described to date, but there utility as antitumor dugs has-for the most part-been limited by their low therapeutic index which can be minimized by antibody-directed delivery. Thus, in view of the combination of the cited references, one of skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody, one would achieve an effective method of treating a B-cell malignancy. Regarding Applicants second article by Hamann et

al, the Examiner has carefully reviewed Hamann et al. and does not dispute Applicants assertions that Hamann et al. teaches that "The contrasting results obtained with the anti-P67.6 and anti-MUC-1 antibody conjugates probably depend more on the physiology of the target cells and the antigen that is targeted than on any specific properties of the antibodies or cytotoxic agent.". However, the Examiner recognizes that the article does not appear to assert an unpredictability or no reasonable expectation of success of treating AML using calicheamicin-antiCD33-antibody conjugates, but instead, appears to focus more on optimizing the choice of linker. Thus, in view of the combination of cited references, it is the Examiner's opinion that one of ordinary skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody, one would achieve an effective method of treating a B-cell malignancy

Claims 134-135 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (US 6,183,744, 2001) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588, of record), as applied to claims 113-121, 124-127, 129-133 and 142-143 above, and in further view of Maloney et al. (Blood 1997; 90: 2188-2195).

Goldenberg in view of Trail et al. teaches a method of treating a B cell malignancy in a patient comprising administering a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a calicheamicin derivative.

Goldenberg in view of Trail et al. does not explicitly teach that the immunoconjugate is administered in combination with Rituximab, an anti-CD20 antibody.

Maloney et al. teach a method of treating low-grade Non-Hodgkin's lymphoma, comprising administering to a patient in need thereof a therapeutically effective amount of Rituximab (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of treating Non-Hodgkin's lymphoma comprising administering an immunoconjugate comprising an anti-CD22 antibody as taught by Goldenberg in view of Trail et al. with Rituximab in view of Maloney et al' teachings that Rituximab is effective at treating Non-Hodgkin's lymphoma because each of the agents have

been individually taught in the prior art for the treatment of lymphoma. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have a reasonable expectation of success that by administering a immunoconjugate comprising an anti-CD22 antibody in combination with Rituximab, one would achieve an effective method of treating a B-cell malignancy.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In response to this rejection, Applicants assert, as discussed above, neither Goldenberg nor Trail et al. teach or describe a method of treating a subject with a B-cell malignancy by administering a composition comprising a calicheamicin-anti-CD22 antibody conjugate alone or in combination with one or more cytotoxic or bioactive agents, and there is no reasonable expectation of success in treating such subjects based on the teachings of Goldenberg in view of Trail et al.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above and incorporated herein.

Claims 145-149 appear to be free of the prior art, but are objected to for being dependent from a rejected independent claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF